Please add new Claims 36 and 37 as follows:

36. (New) The injectable formulation of claim 29, wherein the polypeptide is an anti-vascular endothelial growth factor Fab (anti-VEGF Fab).

37. (New) The injectable formulation of claim 35, wherein the polypeptide is an anti-vascular endothelial growth factor Fab (anti-VEGF Fab).

SUPPORT FOR AMENDMENT

The amendment to claims 17 and 21 is supported by the specification, page 3, line 16. The amendment to claim 20 is supported by the specification, page 14, lines 4-5. Claims 36 and 37 are supported by original claims 29 and 35. Other amended claims have been clarified. No new matter has been added. Upon entry of this amendment, claims 17, 20-23, 25-31 and 33-37 are present and active in the application.

REQUEST FOR RECONSIDERATION

Applicants would like to thank Examiner Chih-Min Kam, and her supervisor, for the courteous and helpful discussion held with applicants' representative on September 12, 2002. During this discussion, it was noted that example 1 of Machida et al. forms a composition for the preparation of particles, that contains solvents such as methylene chloride, which are inappropriate for injection.

The formulation of a biologically active agent with a biodegradable polymer can provide for sustained release of the agent into a patient. However, most of these formulations must be surgically implanted, or can be injected only through a needle having a large diameter. The formulation of biologically active agents with various liquids can provide for the administration of the agent through a needle of standard size, for example a 23-gauge needle or smaller. This can greatly improve patient compliance to the therapy. However, such formulations typically do not provide acceptable control over the rate with which the biologically active agent is released into the patient. The present invention overcomes these problems.

The claimed inv ntion includes an injectable formulation, including hyaluronic acid dissolved in a physiological buffer, and particles, the particles including a biologically active agent and a biocompatible polymeric matrix. This formulation provides for the administration of a biologically active agent into a patient.

The rejection of the claims under 35 U.S.C. 103 over Machida et al. (EP0263490 A2) in view of the Aldrich catalog, is respectfully traversed. Machida et al. uses hyaluronic acid to precipitate particles, but never prepares a formulation for injection that contains the hyaluronic acid dissolved in a physiological buffer.

Machida et al. (EP0263490 A2) describes a method of making a particulate formulation by mixing: (1) an organic phase comprising a biodegradable polymer and a biologically active agent and (2) an aqueous solution of hyaluronic acid (column 4, lines 14-34). Thus, hyaluronic acid is a used as a medium for precipitating the particles containing the active agent. The particles produced by this method are administered by injecting a mixture of the particles with a physiological saline after they have been washed (Example 3, and col. 10, lines 22-29). In Example 1, the particles are precipitated from a mixture including methylene chloride and n-propanol (col. 5, lines 15-40). There is no description of a composition which includes hyaluronic acid dissolved in a physiological buffer, together with particles including a biologically active agent.

The Aldrich catalog shows a 23 gauge syringe needle. There is no description of a composition which includes hyaluronic acid dissolved in a physiological buffer, together with particles including a biologically active agent.

The present invention includes hyaluronic acid dissolved in a physiological buffer. Machida et al. uses hyaluronic acid to cause precipitation, and does not dissolve it in a physiological buffer together with particles including a biologically active agent. The Aldrich catalog has been cited only for showing a 23 gauge syringe needle. Applicants submit that the claimed invention is not obvious over the applied references. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. 112, first and second paragraphs, has been obviated by appropriate amendment.

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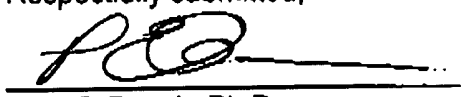
Applicants submit that the present application is in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

17. (Twice Amended) An injectable formulation, comprising:

(a) particles comprising a biocompatible polymeric matrix, the matrix comprising a poly(lactide-co-glycolide);

(b) a biologically active polypeptide dispersed within the matrix; and

(c) an injection vehicle comprising hyaluronic acid dissolved in a physiological buffer.

20. (Twice Amended) A method for administering a biologically active agent, comprising:

injecting the [composition]formulation of claim 17 into a patient in need thereof through a 23-gauge or smaller needle,

wherein the particles have an average diameter of between about 5 and about 200 microns.

21. (Amended) An injectable formulation, comprising:

(a) hyaluronic acid dissolved in a physiological buffer; and

(b) particles, comprising:

(i) a biologically active agent, and

(ii) a biocompatible polymeric matrix.

29. (Twice Amended) The injectable formulation of claim 28, wherein the polypeptide is selected from the group consisting of a growth hormone, a hepatocyte growth factor (HGF), a vascular endothelial growth factor (VEGF), [an anti-vascular endothelial growth factor Fab (anti-VEGF Fab),] a glucagon-like peptide I (GLP-I), a nerve growth factor, an insulin-like growth factor, and an antibody.

30. (Amended) The injectable formulation of claim 21, wherein the concentration of the polymeric matrix [comprising the biologically active agent] is about 1 mg/mL to about 500 mg/mL of formulation.

33. (Amended) The injectable formulation of claim 21, wherein the hyaluronic acid is [selected from the group consisting of] N-acylurea modified hyaluronic acid [and amino acid modified hyaluronic acid].

35. (Amended) The injectable formulation of claim 17, wherein the polypeptide is selected from the group consisting of a growth hormone, a hepatocyte growth factor (HGF), a vascular endothelial growth factor (VEGF), [an anti-vascular endothelial growth factor Fab (anti-VEGF Fab),] a glucagon-like peptide I (GLP-I), a nerve growth factor, an insulin-like growth factor, and an antibody.